

REMARKS

Reconsideration of this application is respectfully requested. Claims 21, 25, 27, 31, 33, and 37 are pending.

Rejections Under 35 U.S.C. §103

Claims 21, 25, 27, 31, 33, and 37 have been rejected under 35 U.S.C. §103 as obvious over Patris, *Int. Clin. Psychopharm.* 11:129-136 (1996) ("Patris") in view of U.S. Patent No. 4,943,590 ("Boegesoe") and U.S. Patent No. 4,079,135 ("Maisey"). The Examiner cites Patris as disclosing administration of citalopram to treat patients with major depression and a MADRS score of 30, but admits that Patris does not disclose escitalopram. The Examiner cites Boegesoe as disclosing that all the 5-HT uptake inhibition activity in racemic citalopram resides in escitalopram, but admits that Boegesoe does not disclose oxalate salts. The Examiner cites Maisey as teaching an antidepressant that can be routinely converted to a crystalline oxalate salt before administration, but admits that Maisey does not disclose escitalopram. From this, the Examiner concludes that it would have been obvious to use crystalline escitalopram oxalate to treat severe depression in patients with a MADRS score of at least 29.

The rejection is traversed, and reconsideration is respectfully requested.

Claims 21, 25, 27, 31, 33, and 37 are not obvious because, *inter alia*, the detrimental impact of R-citalopram on escitalopram in racemic citalopram was neither known nor reasonably predictable, and because the claimed invention is associated with unexpected results.

At the time the present application was filed, one of ordinary skill would have expected escitalopram to be only about twice as potent since it was not known that the R-enantiomer negatively impacts the efficacy of escitalopram at (*see* specification at p. 2, lines 13-14). In fact, this discovery regarding the R-enantiomer was an unexpected surprise to those of ordinary skill in the art. *See also* Jacquot et al., "Escitalopram and citalopram: the unexpected role of the R-enantiomer," *Encephale* 33(2):179-87 (Mar-Apr 2007) Abstract ("[t]he antagonism of escitalopram by R-citalopram was not expected") (copy enclosed as Exhibit A).

In response to Applicant's prior argument that escitalopram is more than twice as potent as its racemate, the Examiner asserts that "potency does not equate to greater efficacy, it only equates to a faster onset of therapeutic activity." See Office Action, p. 2. However, the Examiner's assertion that potency equates to faster onset is both unsupported and incorrect. It is well established that potency relates to efficacy. For instance, "potency" is defined as (STEDMAN'S MEDICAL DICTIONARY 1433 (Lippincott, Williams & Wilkins, 27th ed. 2000) (copy enclosed as Exhibit B):

In therapeutics, the relative pharmacologic activity of a dose of a compound compared with the dose of a different agent producing the same effects; e.g., aspirin and acetaminophen are of equal potency in alleviating headache (same dose required), but ketarolac exhibited greater potency than ibuprofen, as 20 mg of the former is as effective as 400 mg of the latter.

This dictionary definition does not mention speed of onset, and confirms that a drug with a higher potency can be used to achieve the same effect with a lower dose. Hence, Applicant respectfully requests that the Examiner withdraw his incorrect and unsupported assumption that potency equates to faster onset. Moreover, the specification's statement that escitalopram is "substantially more than two times as potent as the racemate" (p. 2, lines 13-15) is evidence of unexpected results as further discussed below.

In particular, the efficacy of escitalopram in treating severe depression in patients with a MADRS score of at least 29 is surprising and unexpected because one of ordinary skill in the art could not have predicted the detrimental influence of R-citalopram in treating depression. As stated in the present specification, the inventors surprisingly discovered that the R-enantiomer in citalopram has a *negative* effect on escitalopram, resulting in citalopram's inferior efficacy (see Specification, p. 2, lines 13-14). None of the cited references discloses or suggests the detrimental influence of the R-enantiomer, or that administration of escitalopram alone would provide the demonstrated superior therapeutic effect as compared to racemic citalopram.

Evidence of these unexpected results are documented in Burke et al., *J. Clin. Psychiatry*, 63(4):331-336 (April 2002) (copy previously submitted with the Response filed November 20, 2006), which describes a study evaluating the efficacy and tolerability of 10 mg/day escitalopram in the treatment of major depressive disorder (MDD) (p. 332, right col.; p. 333, Tables 1 and 2). The

patients in Burke's study received placebo, 10 mg/day escitalopram, 20 mg/day escitalopram, or 40 mg/day citalopram. Those treated with 10 mg/day escitalopram had a baseline MADRS score (mean \pm SD) of 28.0 ± 4.9 (p. 333, Table 1), which means that this group *necessarily* included patients with a MADRS score of at least 29 (as called for in the pending claims) because such scores are well within the recorded standard deviation.

According to Burke, the decreases from baseline in MADRS, HAM-D, HAM-D depressed mood item, CGI-S, and CGI-I scores for the 10 mg /day escitalopram group "were statistically significantly superior to those observed for placebo treatment" (p. 333, Efficacy). Thus, Burke demonstrates a surprising and significant improvement in MDD patients treated with 10 mg/day escitalopram on several different scales. Additionally, Burke points out that 40 mg/day citalopram (which comprises 20 mg/day each of escitalopram and R-citalopram) was not more effective than 10 mg/day escitalopram "on the major efficacy outcome variables at study endpoint, including MADRS, HAM-D, CGI-I, and CGI-S (Table 2)" (p. 333, right col.). Burke further explains that this was an unexpected result by stating (p. 336):

Twice as much escitalopram is administered daily in the 40-mg/day citalopram dose than is administered in the 10-mg/day escitalopram dose, and one might expect from this that citalopram, 40 mg/day, would be more effective than escitalopram, 10 mg/day. This was not the case, however, since actual treatment with escitalopram, 10 mg/day, was at least as effective as citalopram 40 mg/day, on the major efficacy outcome variables (MADRS, HAM-D, CGI-I, and CGI-S), as well as the MADRS response rate.

Since Burke establishes that one of ordinary skill in the art would not have predicted 10 mg/day escitalopram to be significantly better than 40 mg/day citalopram in treating MDD, Burke shows that the claimed invention yields unexpected results. The fact that Burke's data does not appear in the specification and was published after the claimed invention was made is irrelevant and does not negate the value of these findings in the present obviousness determination. *See Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1150 (Fed. Cir. 1983) ("Facts determinable at a later time may serve to evidence nonobviousness as of the time the invention was made."); *see also Richardson-Vicks Inc. v. The Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) (referencing "the well-established rule that 'all evidence of nonobviousness must be considered when assessing patentability'") quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

Furthermore, other studies similarly demonstrate unexpected results. *See, e.g.,* Gorman, *MedWorks Media*, 40-44 (April 2002); Lepola, *Int Clin Psychopharm*, 18(4):211-17 (2003); Moore, *Int Clin Psychopharm*, 20(3):131-37 (2005); Lam, *Pharmacopsychiatry*, 39:180-84 (2006); and Yevtushenko, *Clinical Therapeutics*, 29(11):1-14 (2007). A copy of Lepola was submitted with the Response filed November 20, 2006; copies of Gorman (2002), Moore (2005), and Lam (2006) were submitted with the Response filed September 27, 2007; and a copy of Yevtushenko (2007) was submitted with the Response filed August 7, 2008. Each of these studies confirms that escitalopram) has unexpectedly superior efficacy compared to citalopram in patients suffering from severe depression and having a MADRS score of at least 29. Thus, all of this evidence taken as a whole readily demonstrates the unexpected superiority of the claimed invention.

The Examiner also states that the surprising results disclosed in the specification are “based on arbitrary ‘p’ values.” *See* Office Action, p. 3. However, the Examiner’s statement is incorrect because the disclosed p values are measured numbers (not arbitrary values) that indicate the statistical significance of the results of the clinical study described in the specification. In other words, it is readily apparent that the administrators of the study described in the specification evaluated the patients included in this study and recorded whether a statistically significant improvement was observed in order to determine the p values disclosed in the specification.

Given the foregoing, claims 21, 25, 27, 31, 33, and 37 are not obvious over the cited references. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Conclusion

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: November 24, 2009

Respectfully submitted,

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EXHIBIT A

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1: Encephale. 2007 Mar-Apr;33(2):179-87.

Full text on EM|consulte [] Links
Subscription required []**[Escitalopram and citalopram: the unexpected role of the R-enantiomer]**

[Article in French]

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Citalopram, a selective serotonin reuptake inhibitor, is composed of 2 enantiomers, R-citalopram and S-citalopram, 2 different non-superimposable mirror image forms of the same molecule. Separating these 2 enantiomers has enabled studying their individual properties. Citalopram's pharmacologic activity is centered on the S-enantiomer's high affinity for the serotonin transporter which is twice as high as citalopram's and 30 to 40 times higher than R-citalopram. This leads to an inhibition of serotonin reuptake two times higher for escitalopram compared with citalopram and confirms that citalopram's pharmacologic activity is due to the S-enantiomer. Contrary to what might be expected, the effect of escitalopram (DCI of S-citalopram) is not superimposable on an equivalent dose of citalopram but is superior. Several hypotheses could explain this superiority. First, conversions of the S-enantiomer into the R-enantiomer may occur, but there is no reason why this phenomenon would happen more when both enantiomers are present than when escitalopram is alone. Furthermore, pharmacokinetic studies have shown that S or R configurations are stable in vivo. Second, a particular action of R-citalopram may influence the S-enantiomer's kinetic from intestinal absorption to blood-brain barrier. But concentrations of both enantiomers in the frontal cortex are the same. Therefore, R-citalopram does not interfere with escitalopram's kinetic. Finally, interactions may appear at the synaptic level. Results of experimentation, after in situ injection to the cortex level, confirm that an interaction between the 2 enantiomers takes place at that level. A direct negative interaction of R-citalopram on one or several effectors that create the antidepressive effect seems justified. This negative interaction has been studied in depth. Animal models have shown that the R-enantiomer has no antidepressive potential and when associated with escitalopram prohedonic effects disappear. Escitalopram is more powerful than citalopram in reducing anxiety but the presence of R-citalopram reduces the positive effects of escitalopram. We then may conclude that R-citalopram antagonizes the antidepressive effects of escitalopram and that its presence limits the therapeutic effect and

Related Articles

Review [Escitalopram: a selective inhibitor and allosteric modulator of the serotonin transporter] (Encephale. 2007)

Review Escitalopram versus citalopram: the surprising role of [Encephale. 2004]

[Mechanisms of action of antidepressants: new data from Escitalopram] (Encephale. 2003)

Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent effects in animal models predictive of antidepressant activity (Encephale. 2003)

Review Escitalopram : a review of its use in the management of major depressive and anxiety disorders. (CNS Drugs. 2003)

» See Reviews... | » See All...

Patient Drug Information**Escitalopram (Lexapro®)** Escitalopram is used to treat depression and generalized anxiety disorder (GAD; excessive worry and tension that**Citalopram (Celexa®)** Citalopram is used to treat depression. Citalopram is in a class of antidepressants called selective serotonin

Source: AHFS Consumer Medication Information

Recent Activity

reduces the speed of action of citalopram. The antagonism of escitalopram by R-citalopram was not expected and one hypothesis is that a direct interaction between the 2 enantiomers may occur on a particular site of the serotonin transporter. Results have shown that R-citalopram has a significant affinity only for the allosteric site of the transporter, which regulates the affinity of the ligand for the active site at the origin of serotonin reuptake inhibition. Unlike citalopram, escitalopram's pharmacologic action is not blocked by R-citalopram explaining its greater therapeutic efficacy and more rapid mode of action.

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EXHIBIT B

STEDMAN'S Medical Dictionary

27th Edition

Illustrated in Color



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1 2 3 4 5

potassium

potassium

n. pure cultures. SYN
to or affected by
of the limbs or the
pono, pp. postius.
ended and lowered
ur is developed or
iciency.
namic p. [posture
ility under varying
raphy.
uterus.
ation.
val'vū-lār). Relat-
ficativales.
potābīlis, fr. pono.
01. SEE P. sign.
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any flow of water.
arl-ash. [E. pot-
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f "white lotion."
potassium.
metallic element,
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of the anion. SYN
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mouthwash and
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d urinary alka-
an astringent,
to be handled
c acid, sodium
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dote to copper

p. gluconate, gluconic acid p. salt, used in hypokalemia as a replenisher.
p. guaiacolsulfonate, used as an expectorant.
p. hydroxide, KOH; a strong, penetrating caustic. SYN caustic potash.
p. hypophosphite, formerly believed to have a tonic effect upon the nervous system; may be explosive if triturated or heated with oxidizing agents.
p. iodate, an oxidizing agent and disinfectant.
p. iodide, KI; used as an alternative and expectorant, and in certain mycoses.
p. metaphosphate, a pharmaceutical aid (buffer).
monobasic p. phosphate, used as a urinary acidifier and buffer.
p. nitrate, sometimes used as a diuretic and diaphoretic; formerly it was included in asthmatic powders containing stramonium leaves. SYN niter, saltpeter.
penicillin G p., SEE penicillin G potassium.
p. perchlorate, occasionally used, as an alternative to a thiouracil derivative, in the control of hyperthyroidism.
p. permanganate, a strong oxidizing agent, used in solution as an antiseptic, and deodorizing application for foul lesions, and formerly as a gastric lavage in poisoning from morphine, strychnine, aconite, and picrotoxin; in electron microscopy, it stains cytomembranes well and gives results similar to lead hydroxide staining; also used as a fixative (Luft).
p. phosphate, a mild saline cathartic and diuretic. SYN dibasic p. phosphate, dipotassium phosphate.
p. rhodanate, SYN p. thiocyanate.
p. sodium tartrate, a mild saline cathartic, used as an ingredient in compound effervescent powders. SYN Rochelle salt, Seignette salt, sodium potassium tartrate.
p. sorbate, 2,4-hexadienoic acid potassium salt; a mold and yeast inhibitor, used as a preservative.
p. succinate, a deliquescent powder used as a hemostatic.
p. sulfate, an obsolete laxative.
p. sulfocyanate, SYN p. thiocyanate.
p. tartrate, a mild purgative and diuretic. SYN soluble tartar.
p. thiocyanate, formerly used in the treatment of essential hypertension and as a reagent in the detection of copper, iron, and silver. SYN p. rhodanate, p. sulfocyanate.
potassium-39 (³⁹K). Most abundant, nonradioactive isotope of potassium; accounts for 93.1% of natural potassium.
po-tas-si-um-40 (⁴⁰K). A naturally occurring (0.0117%) radioactive potassium isotope; beta emitter with half-life of 1.26 billion years; chief source of natural radioactivity of living tissue.
po-tas-si-um-42 (⁴²K). An artificial potassium isotope; beta emitter with half-life of 12.36 hr, used as a tracer in studies of potassium distribution in body fluid compartments and in localization of brain tumors.
po-tas-si-um-43 (⁴³K). An artificial potassium isotope; a beta emitter with a half-life of 22.3 hr, used as a tracer in myocardial perfusion studies.
po-ten-cy (pō'ten-sē). 1. Power, force, or strength; the condition or quality of being potent. 2. Specifically, sexual p. 3. In therapeutics, the relative pharmacologic activity of a dose of a compound compared with the dose of a different agent producing the same effects; e.g., aspirin and acetaminophen are of equal potency in alleviating headache (same dose required), but ketarolac exhibits greater potency than ibuprofen, as 20 mg of the former is as effective as 400 mg of the latter. [L. *potentia*, power]
sexual p., the ability to carry out and consummate sexual intercourse, usually referring to the male.
po-tent (pō'tent). 1. Possessing force, power, strength. 2. Indicating the ability of a primitive cell to differentiate. SEE ALSO totipotent, pluripotent, unipotent. 3. In psychiatry, possessing sexual potency.
po-ten-tial (pō'ten-shāl). 1. Capable of doing or being, although not yet doing or being; possible, but not actual. 2. A state of tension in an electric source enabling it to do work under suitable conditions; in relation to electricity, p. is analogous to the temperature in relation to heat. [L. *potentia*, power, potency]

action p., the change in membrane p. occurring in nerve; muscle, or other excitable tissue when excitation occurs.
after-p., SEE afterpotential.
bioelectric p., electrical p.'s occurring in living organisms.
biotic p.; a theoretical measurement of the capacity of a species to survive or to compete successfully.
brain p., the electrical charge of the brain as compared to a point on the body; the p. may be steady (DC p.) or may fluctuate at specific frequencies when recorded against time, giving rise to the electroencephalogram.
brainstem auditory evoked p., responses triggered by click stimuli, which are generated in the acoustic nerve and brainstem auditory pathways; recorded over the scalp.
chemical p. (μ), a measure of how the Gibbs free energy of a phase depends on any change in the composition of that phase.
cochlear p., SYN cochlear microphonic.
compound action p., the combined p.'s resulting from activation of the auditory division of the eighth cranial nerve.
demarcation p., the difference in p. recorded when one electrode is placed on intact nerve fibers or muscle fibers and the other electrode is placed on the injured ends of the same fibers; the intact portion is positive with reference to the injured portion. SYN injury p.
early receptor p. (ERP), a voltage arising across the eye from a charge displacement within photoreceptor pigment, in response to an intense flash of light.
endocochlear p., the standing direct current p. in the endolymph relative to the perilymph, measuring positive 80 mV.
evoked p., an event-related potential, elicited by, and time-locked to, a stimulus. SEE ALSO evoked response.
excitatory junction p. (EJP), discrete partial depolarization of smooth muscle produced by stimulation of excitatory nerves; similar to small end-plate p.'s; summate with repeated stimuli.
excitatory postsynaptic p. (EPSP), the change in p. that is produced in the membrane of the next neuron when an impulse that has an excitatory influence arrives at the synapse; it is a local change in the direction of depolarization; summation of these p.'s can lead to discharge of an impulse by the neuron.
generator p., local depolarization of the membrane p. at the end of a sensory neurone in graded response to the strength of a stimulus applied to the associated receptor organ, e.g., a pacinian corpuscle; if the generator p. becomes large enough (because the stimulus is at least of threshold strength), it causes excitation at the nearest node of Ranvier and a propagated action p.
inhibitory junction p. (IJP), hyperpolarization of smooth muscle produced by stimulation of inhibitory nerves.
inhibitory postsynaptic p. (IPSP), the change in p. produced in the membrane of the next neuron when an impulse that has an inhibitory influence arrives at the synapse; it is a local change in the direction of hyperpolarization; the frequency of discharge of a given neuron is determined by the extent to which impulses that lead to excitatory postsynaptic p.'s predominate over those that cause inhibitory postsynaptic p.'s.
injury p., SYN demarcation p.
membrane p., the p. inside a cell membrane, measured relative to the fluid just outside; it is negative under resting conditions and becomes positive during an action p. SYN transmembrane p.
myogenic p., action p. of muscle.
oscillatory p., the variable voltage in the positive deflection of the electroretinogram (β -wave) of the dark-adapted eye arising from amacrine cells.
Ottoson p., SYN electroolfactogram.
oxidation-reduction p. (E_0), the p. in volts of an inert metallic electrode measured in a system of an arbitrarily chosen ratio of [oxidant] to [reductant] and referred to the normal hydrogen electrode at absolute temperature; it is calculated from the following equation; where R is the gas constant expressed in electrical units, T the absolute temperature (Kelvin), n the number of electrons transferred, F the faraday, and E_0 the normal symbol for the p. of the system at pH 0; for biologic systems, E_0' is often used (in which pH = 7). Cf. Nernst equation. SYN redox p.

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